Opinion

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ADULT STEM CELLS

By Dr Greg Pike

In the past couple of years the scientific, bioethical, and political communities have been as much in a spin about stem cells as they have about cloning. The reason for the excitement began with a report of the isolation and culturing of human embryonic stem (ES) cells in late 1998[1]. This research, using a human IVF embryo, opened up exciting possibilities in cell therapies for the treatment of Parkinson's, Alzheimer's, diabetes and many other diseases. Even more exciting was the prospect that a cloned embryo could be produced and the ES cells extracted and used to treat the individual from whom the clone was made, thus avoiding problems with tissue rejection. This proposal was termed 'therapeutic cloning', a label wholesome enough to ease the public's disquiet about cloning. After all, one can never have enough therapy.

The cells, extracted from the inner cell mass of 5-6 day old embryos, would in the normal course of events continue development to become all of the 200 or so different cell types making up the human body. It is therefore not surprising that so much hope is pinned on these universal cells that they might be able to be directed into a chosen cell type at will for a particular medical treatment.

The ethical catch however, is obvious. Human embryonic stem cells involve the destruction of living human embryos. But what if there were a viable, equally promising alternative not reliant upon the creation and destruction of human embryos. And what if significantly encouraging research was already underway and steadily progressing?

A recent editorial entitled "Overexcitement on embryo stem cells" in what is arguably the world's most prestigious medical journal *The Lancet*, concluded with the following words:

In just a few days a moral issue that ought to trouble even those with no religious beliefs has been taken over by scientists, by politicians, and by money. The irony is that by the time the matter is resolved it may no longer be relevant. If stem cells do turn out to be a significant source of therapeutic agents they could come not from human embryos but from alternatives such as reprogrammed adult cells.[2]

While embryonic stem cells are extremely versatile cells, adult stem cells may be similarly potent. Their use does not raise the immediate ethical dilemmas posed by the

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[1] Thompson, J.A. *et al*., Embryonic stem cell lines derived from human blastocysts. *Science*, 6 November 1998, **282**:1145-1147.

[2] Editorial, Overexcitement on embryo stem cells, *The Lancet*, 26 August 2000, **356**(9231):693.

use of ES cells. Malcolm Moore from the Memorial Sloan-Kettering Cancer Center in New York has pointed out that:

Lineage-defined progenitor cells in adult tissues [adult stem cells] may be more plastic than hitherto thought. They might have the capacity to de-differentiate, or be reprogrammed, becoming totipotent stem cells.[3]

The promise inherent in adult stem cells may provide a way out of the current conundrum. As the United States National Bioethics Advisory Commission (NBAC) concluded:

Because of ethical and moral concerns raised by the use of embryos for research purposes it would be far more desirable to explore the direct use of human cells of adult origin to produce specialized cells or tissues for transplantation into patients.[4]

Adult stem cells may be found in brain, pancreas, liver, bone marrow, blood, muscle, skin and other sites. They typically give rise to a limited number of specialised cells within their tissue of origin. But recent studies indicate that they are far more versatile, and "perhaps in some cases have a developmental repertoire close to that of ES cells."[5]

Studies at Harvard Medical School have shown that mouse neural stem cells can be injected into the brains of mice with a degenerative disorder, the abnormal cells being replaced by a large number of normal cells.[6] In an interesting twist, neural stem cells could be coerced into becoming blood cells, including cells carrying out an immune function such as B and T lymphocytes.[7] Moreover, the potency of neural stem cells has recently been further unveiled in animal studies where these cells have been able to promote spinal cord repair.[8]

But perhaps the most exciting prospects for employing these cells is in Parkinson's disease. In a separate study, adult neural stem cells were grafted into a specific brain site in rats that had been developed as a model of human Parkinson's disease. Some time later, Parkinsonian symptoms diminished, leading to a limited recovery of function.[9] This type of cell has recently been isolated in humans and behaves similarly to its equivalent in the mouse.[10]

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[3] Malcolm Moore, "Turning Brain into Blood" – Clinical Applications of Stem-Cell Research in Neurobiology and Hematology. *The New England Journal of Medicine*, 19 August 1999, **341(8)**:605-607.

[4] NBAC 1997, 30-31.

[5] Clarke, D. L. *et al*., Generalized Potential of Adult Neural Stem Cells. *Science*, 2 June 2000, **288**:1660-1663.

[6] Reported by Abi Berger, Neural stem cells successfully transplanted. *British Medical Journal*, 12 June 1999, **318**:1575.

[7] Bjorson, C. R. *et al*., Turning brain into blood: a hematopoietic fate adopted by adult neural stem cells *in vivo*. *Science*, 22 January 1999, **283**:534-7.

[8] Steve S.W. Han & Itzhak Fischer, Neural Stem Cells and Gene Therapy: Prospects for Repairing the Injured Spinal Cord. *Journal of the American Medical Association*, 3 May 2000, **283**(17):2300-2301.

[9] Studer, L. *et al*., Transplantation of expanded mesencephalic precursors leads to recovery in Parkinsonian rats. *Nat. Neurosci*. 1998, **1**:290-295.

[10] Svendsen, C. N. *et al*., Human neural stem cells: isolation, expansion and transplantation. *Brain Pathol.* 1999, **9**:499-513.

A recent study in mice showed that adult pancreatic stem cells could be removed, grown in culture and then transplanted into a strain of diabetic mice, thereby reversing the diabetic state[11]. The researchers are confident, based upon preliminary experiments with human tissue, that similar results may be obtained in humans, one day perhaps bringing an end to daily insulin injections.

More recent research in Sweden that took many by surprise, has shown that mouse neural stem cells can be nurtured to become heart, liver, lung, intestine, kidney, muscle, and other tissues.[12] Speaking of the research, Professor Richard Gardner of Oxford University, who chaired a Royal Society group on therapeutic cloning, said:

I think therapeutic cloning is not terribly realistic. This other approach of reprogramming later cells makes sense.[13]

Other adult stem cells, such as mesenchymal stem cells from bone marrow, share a similar broad repertoire. In studies conducted by Catherine Verfaillie at the University of Minnesota, Minneapolis,[14] mesenchymal stem cells have been shown to specialise into neural, cartilage, bone, fat, and muscle cells. Furthermore, not only does Verfaillie consider the cells to be " … almost like ES cells", but she says her cells are "better behaved" in that they are more stable than ES cells and less likely to spontaneously differentiate into a variety of cell types in an uncontrolled fashion.

Yet another type of adult stem cell, the haematopoietic stem cell, which typically gives rise to blood cells, has been shown to differentiate into a variety of neural cells[15], opening up the prospect of a more accessible origin for adult stem cells for use in cell therapy. These well-studied cells have also been injected into mice developed as a model for Duchenne's muscular dystrophy, leading to partial restoration of the missing protein in affected muscle.[16]

In summary, there is no shortage of interesting research being conducted on adult stem cells, and no shortage of promising findings, some already drawing close to trials in humans. What's more, biotechnology companies worldwide are investing more time and money in adult stem cells than ES cells, suggesting that there are many in the industry who consider adult stem cells the better way to go.[17]

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[11] Reported by Abi Berger, Transplanted pancreatic stem cells can reverse diabetes in mice. *Science*, 18 March 2000, **320**:736.

[12] Clarke, D. L. *et al*., Generalized Potential of Adult Neural Stem Cells. *Science*, 2 June 2000, **288**:1660-1663.

[13] Cited by Roger Highfield in *Study queries the need for therapeutic cloning*. Daily Telegraph Internet download. www.telegraph.co.uk

[14] Reported by Gretchen Vogel, Can Old Cells Learn New tricks? *Science*, 25 February 2000, **287**:1418-1419.

[15] Eglitis, M. A. & Mezey, E. Hematopoietic cells differentiate into both microglia and macroglia in the brain of adult mice. *Proc. Natl. Acad. Sci. U.S.A.*, 1997, **94**:4080-4085.

[16] Gussoni, E. *et al*., Dystrophin expression in the mdx mouse restored by stem cell transplantation. *Nature*, 23 September 1999, **401**(6751):390-394.

[17] Eliot Marshall, The Business of Stem Cells. *Science*, 25 February 2000, **287**:1419-1421.

Even though these studies are beginning to reveal that adult stem cells have a similar if not equivalent potential to ES cells, it is sometimes argued that ES cells are much easier to access compared with pursuing the more arduous path of isolating adult stem cells. In reality obtaining ES cells only seems 'easier', because to obtain them, complex, expensive and sometimes rather 'uneasy' practices in reproductive technology are utilized. Even so, the fact that many laboratories worldwide routinely isolate, multiply and transplant a variety of adult stem cells, suggests that any difficulties are readily being overcome.

In the final analysis, perhaps the seemingly obvious outcomes of ES cell research will be supplanted by more effective and morally acceptable research using adult stem cells. In the serendipitous world of scientific investigation, it would not be the first time that less conspicuous or quiet-achiever research turns out to be the most fruitful approach for medical therapeutic application.